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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/662,061	09/12/2003	Christopher J. Horvath	1855.1069-006	1933

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HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/662,061	HORVATH ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 18-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of an anti-CD18 antibody that inhibits binding of ICAM-1 as the first therapeutic agent (E); the species of anti-CCR2 antibody that inhibits binding of MCP-1 as the second therapeutic agent (H); and angioplasty as the species of vascular procedure is acknowledged in the Reply To Restriction Requirement, filed 12/20/06.

The examiner apologizes for any inconvenience to applicant in the confusion concerning elections of a "cytokine" or "cancer therapeutic agent", which were made in error.

Claims 1-39 are pending.

Applicant indicates that claims 1-3, 5-8, 10, 12, 14, 16, 18, 22, 23 and 34-39 read on the elected invention.

However, upon a review of the broadest reasonable interpretation of the claims, including applicant's elected species above,

It appears that claims 1-16 and 18-39 read on the elected invention.

For example, claims 4 and 9, drawn to a first therapeutic agent is a cellular adhesion molecule antagonist binds an integrin, binds CD18 read on the elected species of an anti-CD18 antibody that inhibits binding of ICAM-1.

Also, the species of anti-CCR2 antibody that inhibits binding of MCP-1 as the second therapeutic agent appears to read on claim 11, as cell adhesion molecule antagonist in that the inhibiting CCR2 would have properties encompassing this limitation, even though anti-CCR2 antibodies do not bind an integrin/cell adhesion molecule per se.

Further, anti-CCR2 antibodies read on the limitation of "a CC chemokine receptor" in claims 13 and 15.

Given the well known use of stents in cardiovascular intervention procedures as well as the complications of stenosis and restenosis associated with stents in such procedures, these claims have been included as well. See the teachings of Rogers et al. (US 2002/0006401) below.

Therefore, 1-16 and 18-39 read on the elected invention and are under consideration in the instant application.

It is noted that applicant's election of an anti-CD18 antibody that inhibits binding of ICAM-1 as the first therapeutic agent (E) appears to read on anti-CD18 antibodies, particularly the IB4 specificity.

However, it is noted that LFA-1 is a CD11a/CD18 integrin and LFA-1 is a β2 integrin.

Applicant is invited to clarify the elected species.

Claim 17 has been withdrawn from consideration as being drawn to a nonelected species.

2. It appears that the effective filing date of the instant claims is deemed to be the filing date of priority application USSN 09/528,267, filed 3/17/2000.

3. Applicant should amend the first line of the specification to update the status (and relationship) of the priority documents.

USSN 09/809,739 is now U.S. Patent No. 6,663,863.

4. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ® or ™ symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

5. Claims 1-16 and 18-39 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-16 and 18-39 are indefinite in the recitation of "adhesion molecule antagonist" and "antagonist of CCR2 function" because the metes and bounds of the claimed "antagonistic properties or function" are ill-defined and ambiguous, which renders the claims indefinite. The nature or parameters of the claimed "antagonists" is not defined by the claims and the specification does not provide a standard for ascertaining the requisite degree or direction and, in turn, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention or the parameters by which to determine said metes and bounds.

Applicant is invited to amend the claims to recite a testable function(s) supported by the specification as filed to obviate this rejection.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-16 and 18-39 are rejected under 35 U.S.C. § 103(a) as being unpatentable over LaRosa (U.S. Patent No. 6,312,689) (1449; #AH3) AND Rogers et al. (US 2002/0006401) in further view of Daugherty et al. (U.S. Patent No. 6,797,492), Strom et al. (in Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996; see pages 451-456) and the well known recombinant techniques to produce recombinant antibodies known and practiced at the time the invention was made as acknowledged on pages 16-20 of the instant specification.

LaRosa teaches methods of inhibiting stenosis or restenosis, which results from vascular intervention such as surgical, therapeutic or mechanical intervention, including angioplasty (e.g. see entire document, including column 24, lines 10-26) with antagonistic anti-CCR2 antibodies and antibody fragments thereof, including the ID9 and 8G2 antibodies (e.g., see columns 7-8, columns 10-11) as well as combination therapy (e.g., see columns 25-26, overlapping paragraph) (see entire document, including Summary of the Invention, Detailed Description of the Invention and Claims).

In addition, LaRosa teaches the known chemoattractant and activating properties, including stimulation of chemotaxis, exocytosis or inflammatory mediator release by leukocytes and integrin activation, of the chemokines (e.g., see column 1, paragraph 1; columns 6-7, overlapping paragraph; column 22, paragraphs 2-3) as well as inhibiting leukocyte trafficking in a mammal via chemokine / CCR2-specific antagonists / antibodies (e.g., see colum 23, paragraph 1).

Rogers et al. teach methods of inhibiting stenosis or restenosis, which results by vascular surgery, including angioplasty and stents (e.g. see Abstract and Background of the Invention and paragraphs [0070] – [0075]), with integrin antagonists, including CD18-specific antagonists and LFA-1-specific antibodies (e.g., see paragraphs [0013], [0026], [0031] – [0032], [0033]-[0038]) (see entire document, including Background of the Invention, Summary of the Invention, Detailed Description of the Invention and Claims).

Note that LFA-1 was a known CD11a/CD18 integrin that binds ICAM-1 (CD54).

Alternatively, CD18-specific antagonists, including the IB4 anti-CD18 antibody specificity was known at the time the invention was made, as taught by Daugherty et al. (see entire document). In addition to the teachings of humanizing the IB4 antibody (see entire document), Daugherty et al. also teach the known use of anti-CD18 antibodies in inhbiting the influx and migration of leukocytes expressing CD18 (see columns 12-13, overlapping paragraph).

In addition to the teachings above, it was known at the time the invention was made that the use of immunosuppressive therapy relies upon a number of basic principles as set forth in Strom et al. These principles include that different agents are used, each of which is directed at a different molecular target and aimed at interrupting several discrete stages in the immune activation pathway (e.g. see page 451 and Figure 36.1). Also, additive-synergistic effects are achieved through the application of each agent at a relatively low dose, thereby limiting the toxicity of each individual agents while increasing the total immunosuppressive effect (see page 451, column 1, paragraph 2).

Recombinant techniques to produce recombinant antibodies known and practiced at the time the invention was made as acknowledged on pages 16-20 of the instant specification. Also, see columns 9-11 paragraphs of LaRosa and paragraphs [0037] – [0038] of Rogers et al. for the well known methods of recombinant and humanized antibodies at the time the invention was made, including columns 10-11, overlapping paragraph of LaRosa in the context of recombinant or humanized ID9 and 8G2 CCR2-specific antibodies. In addition. Daugherty et al. teach recombinant means of producing humanized antibodies of interest, including anti-CD18 antibodies /(see entire document).

Although LaRosa is silent about the exact sequences of the CCR2-specific antibodies taught in LaRosa (ID9 and 8G2), the recombinant techniques and computer analyses of CDR grafting as known and practiced at the time the invention was made, as acknowledged on pages 16-20 of the instant specification (also, see columns 9-11 paragraphs of LaRosa and paragraphs [0037] – [0038] of Rogers) would have resulted in the same or very nearly the same structural and functional characteristics of the instant claims since both the references and instant invention use the same techniques, the same antibody specificities and the same goals. The claimed functional limitations encompassed by the claims would be expected properties of selecting for ID9 and/or 8G2 CCR2-specific recombinant or humanized antibodies to antagonize CCR2-mediated functions in order to inhibit stenosis or restenosis. The claims drawn to specifically defined CDR sequences are obvious since the record does not contain any evidence that the cell lines differ in any significant manner or produce antibodies that differ in any significant aspect from ID9 and/or 8G2 CCR2-specific antibodies / hybridomas that one of ordinary skill in the art would expect to generate using ID9 and/or 8G2 CCR2-specific antibodies and hybridomas as the starting materials in the basic methods of generating recombinant / humanized antibodies of said antibodies. There appears no evidence that the use of various sources of framework amino acids would differ in an unexpected or distinct manner from those available to the ordinary artisan at the time the invention was made.

Similarly, the teachings of Daugherty et al. teach the same or render obvious the claimed sequences of the recombinant IB4 CD18-specific antibodies, given the same starting materials and known recombinant methods of producing recombinant or humanized antibodies of interest at the time the invention was made by the ordinary artisan.

The ordinary artisan was motivated to employ recombiant antibodies such as humanized antibodies in therapeutic regimens to take advantage of recombinant means of producing homogeneous antibodies of interest as well as to diminish immunogenicity of therapeutic antibodies in human therapeutic regimens.

Given the teachings by LaRosa and Rogers et al. as well as the well known practice of combination therapy in immunosuppression, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ both anti-CCR2 antibodies and anti-LFA-1 antibodies, given the expressed teachings to treat stenosis and restenosis with said antagonists at the time the invention was made. The motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose. See MPEP 2144.06. Further, Strom et al. provides the known motivation and expectation of success, including additive and synergistic results, in combining immunosuppressants targeting discrete molecular targets, as well as limiting the toxicity of immunosuppression.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR § 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR § 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR § 3.73(b).

9. Claims 1-16 and 18-39 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,663,863 (1449; #A9).

Although the recitation of the instant and patented claims differ, all of the instant and patented claims are drawn to the same or nearly the same combination of anti-CD18 antibodies and anti-CCR2 antibodies in the treatment of stenosis and restenosis. The patented claims anticipate or render obvious the instant claims.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, Ph.D., J.D.
Primary Examiner
Technology Center 1600
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